

Writing Prescriptions for Immunotherapy

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Potential Conflicts:

- Dr. Martin
 - None

Learning Objectives

The participant will be able to:

- 1. explain the differences between standardized and non-standardized extracts;
- 2. compose a therapeutic mix for immunotherapy through review of the literature;
- 3. write a prescription for immunotherapy that contains effective doses of each component; and
- 4. use current guidelines to improve the safety and effectiveness of immunotherapy in the office.

Practice Parameters for IT

- Initially published in Ann Allergy 2003;90(1)
 - Defined extracts as diagnostic
 - Defined “maintenance concentrate” as a vaccine
 - Estimated effective doses
 - Standardized labeling
- Second Update in JACI. 2007; 120(3)
 - Instead of vaccines now called immunotherapy extracts
 - Effective doses further defined
 - Cross-reactivity patterns refined
 - Compatibility refined
 - Patient vials rather than off the board
 - Standardized forms for skin testing, IT prescriptions and delivery



Practice Parameters for IT

Third update

- Update published in 2011
 - New requirements for extract preparation
 - USP 797
 - New indications for immunotherapy
 - Further defined responses to reactions to immunotherapy
 - Medications and immunotherapy reviewed
 - Expanded discussion of SLIT

Allergen extracts as Compounding Sterile Preparations

TABLE VIII. USP Chapter 797 sterile compounding standards for allergy vaccine preparation^{378,379}

Allergen extracts as compounding sterile preparations (CSPs) are single- and multiple-dose intradermal or subcutaneous injections that are prepared by specially trained physicians and personnel under their direct supervision. Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all CSP Microbial Contamination Risk Levels in this chapter only when all of the following criteria are met:

1. Before beginning compounding activities, personnel perform a thorough hand-cleansing procedure by removing debris from under fingernails (using a nail cleaner under running warm water), followed by vigorous hand and arm washing to the elbows for at least 30 seconds with either nonantimicrobial or antimicrobial soap and water.
2. Compounding personnel wear hair covers, facial hair covers, gowns, and face masks.
3. Compounding personnel perform antiseptic hand cleansing with an alcohol-based surgical hand scrub with persistent activity.
4. Compounding personnel wear powder-free sterile gloves that are compatible with sterile 70% isopropyl alcohol before beginning compounding manipulations.
5. Compounding personnel disinfect their gloves intermittently with sterile 70% isopropyl alcohol when preparing multiple allergenic extract as CSPs.
6. Ampule necks and vial stoppers on packages of manufactured sterile ingredients are disinfected by careful wiping with sterile 70% isopropyl alcohol swabs to ensure that the critical sites are wet for at least 10 seconds and allowed to dry before they are used to compound allergen extract as CSPs.
7. The label of each multidose vial of allergen extract as CSPs lists the name of one specific patient, a beyond-use date, and a storage temperature range that is assigned based on the manufacturer's recommendations or peer-reviewed publications.
8. Single-dose allergen extract as CSPs shall not be stored for subsequent additional use.

A copy of the complete USP Chapter 797 guidelines can be accessed at <http://www.usp.org/USPNF/pf/generalChapter797.html>.

Units

- Weight per volume (w/v) = grams per mL
(note that 1:10=1/10)
- Protein nitrogen units (PNU/mL) = mg protein per mL
- Allergy units (AU/mL) = potency of reference vials at the FDA
- Bioequivalent allergy units (BAU/mL) = potency that gives 50mm erythema
- Micrograms major allergen (mcg/mL)
- Histamine equivalent prick (HEP)

Types of Extract

- Aqueous
 - 50% glycerine
 - 3% HSA
- Allergoid
- Polymerized
- T-cell peptide
- Immunostimulatory Sequences (eg: Allergen-CPG)

General Rules of Thumb

- Ideally use patient-specific vials
 - Individualized to each patient with identifiers
 - Multipatient vials
 - Off the board
- Include an effective dose of each component
- Avoid mixing incompatible extracts
- Avoid inclusion of cross-reacting antigens

Esch JACI 2008;122:659-660

Potency of currently available manufacturer's extracts

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; BAU, bioequivalent allergy unit; PNU, protein nitrogen unit.

*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

Potency of Available Extracts

- Elm 1/10 W/V
- Maple 1/10 W/V
- Bermuda Grass: 10,000 AU/ml
- Timothy grass 100,000 AU/ml
- Short Ragweed: 1:10-1:20 wt/vol
- Alternaria 20,000 PNU/ml
- D. farinae 10,000 AU/ml
- Cat 5,000 and 10,000 BAU/ml
- Dog 20,000 PNU/ml OR
- Dog AP 140 mcg/mL

Probable effective dose range for allergen extracts: US units

<u>Antigen</u>	<u>Labeled potency or concentration</u>	<u>Probable effective dose range</u>
Dust mites: (D farinae and D pteronyssinus)	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 mg of Amb a 1
(Concentration of Amb a 1 is on the label of wt/vol extracts)		1000-4000 AU
<u>Nonstandardized extracts</u>		
dog 1:10 to 1:100 wt/vol		15 mcg of Can f 1
Other extracts	1:10 to 1:40 wt/vol or	2.5 to 10mg
	10,000-40,000 PNU/mL	Highest tolerated dose

Write a Prescription

- Skin test pos.

- Elm
- Maple
- Ragweed
- Timothy grass
- Bermuda grass
- D farinae
- B. germanica
- Alternaria
- Cat
- Dog

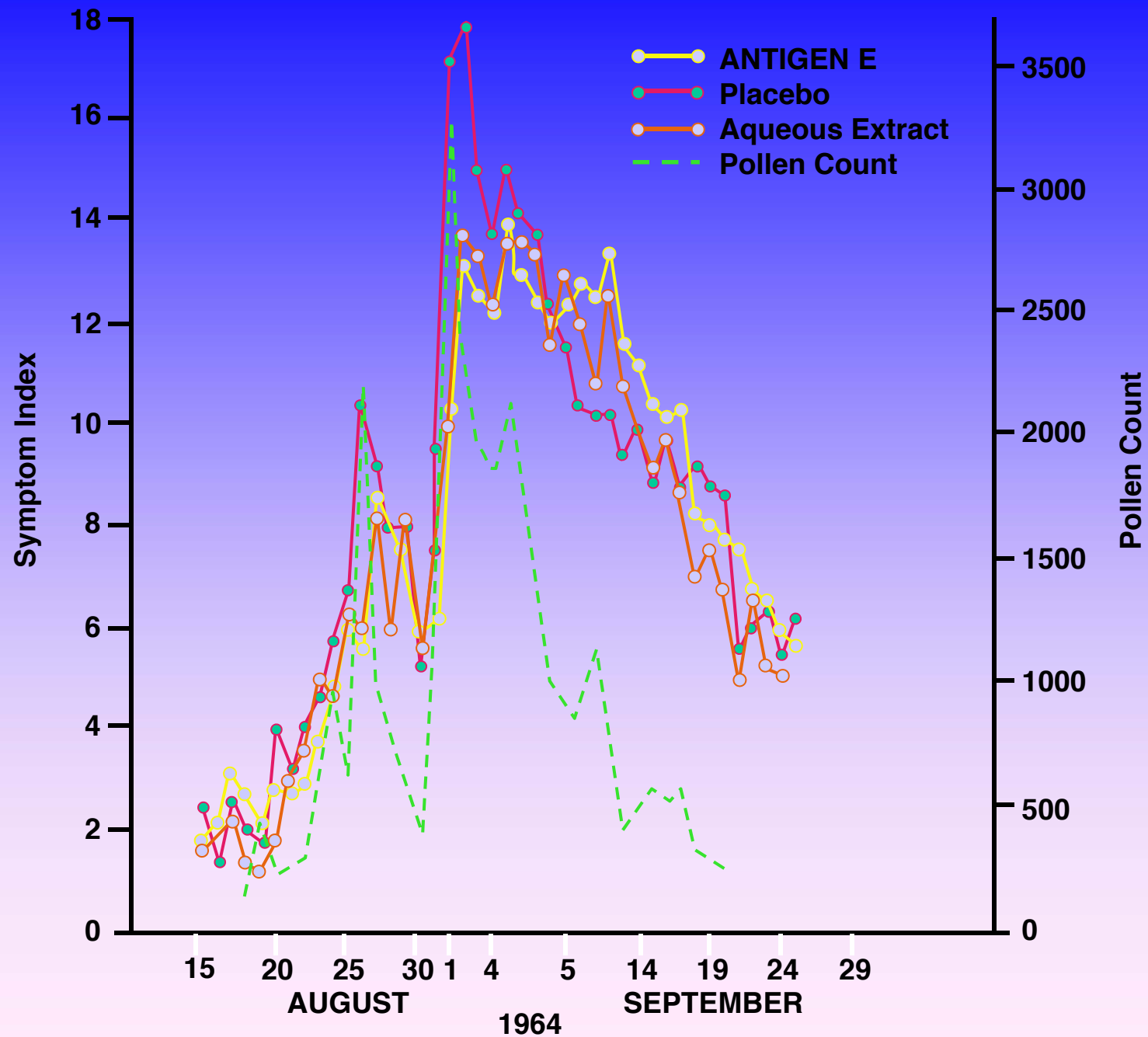
Vial:							
Number	Antigen	Conc of Mfr's Extract	Units	Volume added to extract	Final Concentration	Injected Dose	Units
1	Elm	10	w/v				
2	Maple	10	w/v				
3	S. Ragweed	10	w/v				
4	Timothy	100,000	BAU/ml				
5	Bermuda	10,000	AU/ml				
6	D. farinae	10,000	AU/ml				
7	B. germanica	10	w/v				
8	Alternaria	10	w/v				
9	Cat	10,000	BAU/ml				
10	Dog AP	140	mcg/ml				
11							
12							
	Diluent						
		Total Volume		5.0			
		Injection Volume		0.5			

IT works and it is specific to allergen
Let's start with ragweed

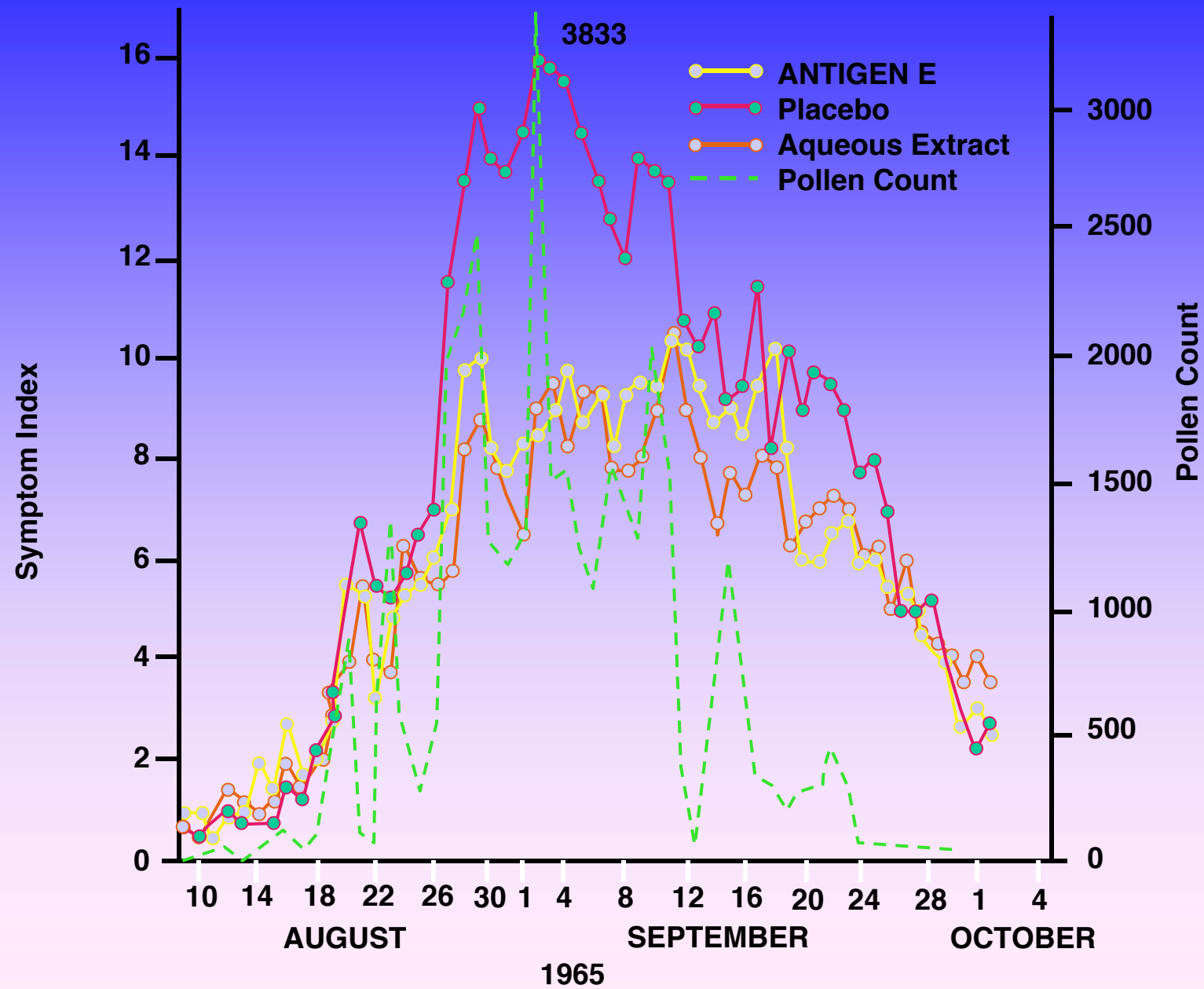
Formula with ragweed

The Math

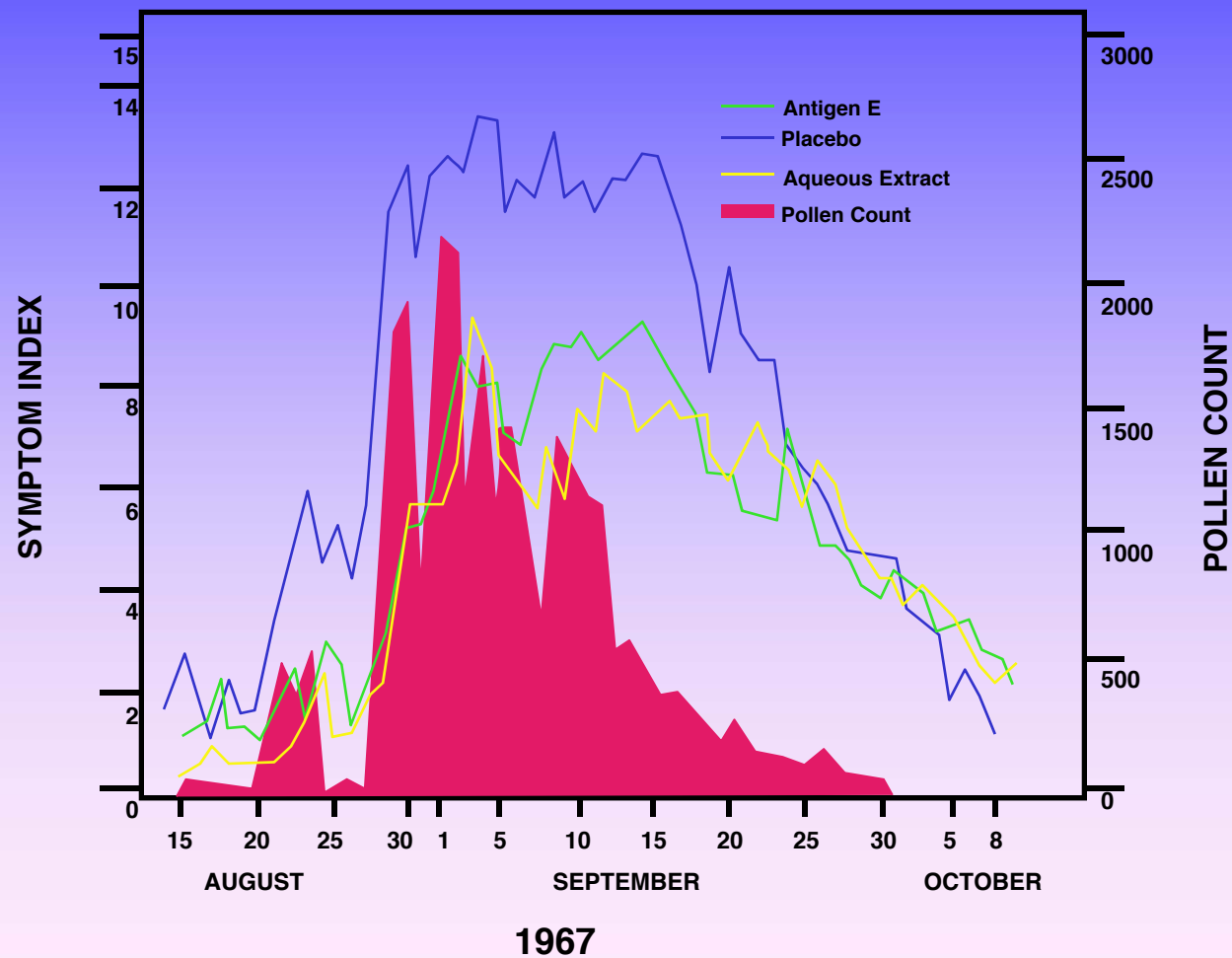
- Concentration X Volume = Dose
- $10,000 \text{ BAU/ml} \times 0.5 \text{ mL} = 5,000 \text{ BAU}$
- $1:10 \text{ (w/v)} = 1 \text{ gm}/10 \text{ mL} = 100 \text{ mg/mL}$
 - Therefore: $1:10 \times 0.5 \text{ mL} = 50 \text{ mg}$

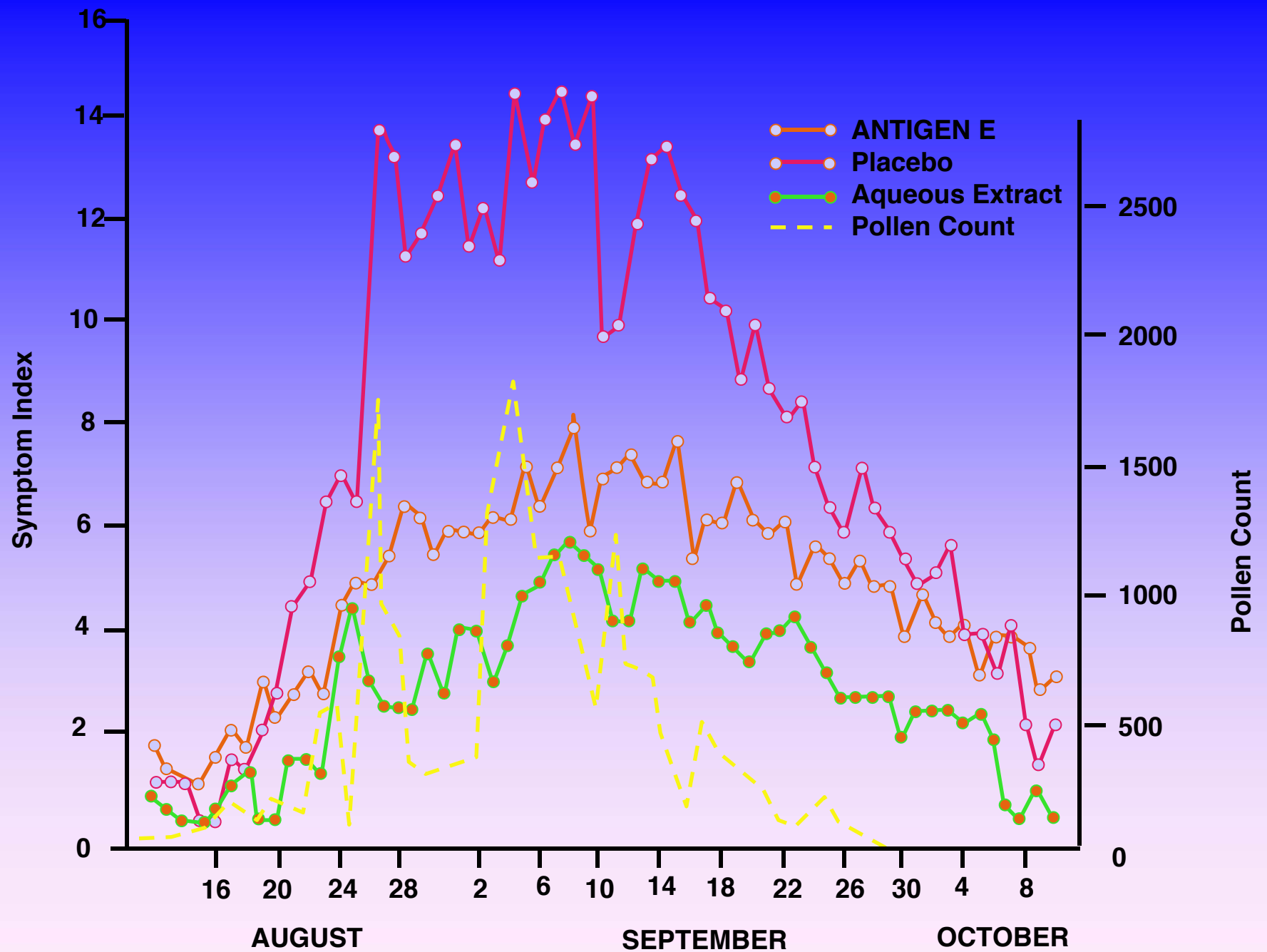


Norman J. A. 1968;42:93



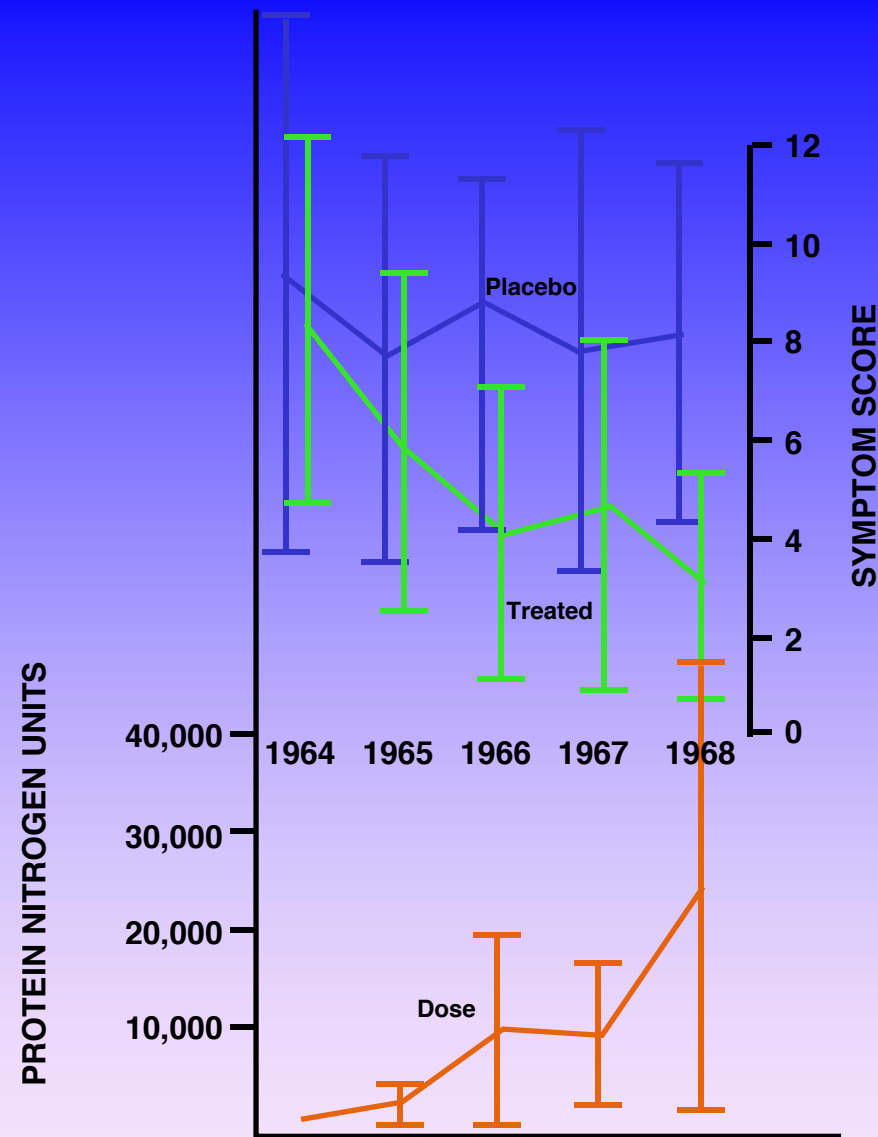
Journal of Allergy and Clinical Immunology





Norman JACI 1971;47:273

1968



Norman JACI; 65:87

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7	B. germanica	10	w/v				
8	Alternaria	10	w/v				
9	Cat	10,000	BAU/ml				
10	Dog AP	140	mcg/ml				
11							
12							
	Diluent						
		Total Volume		5.0			
		Injection Volume		0.5			

$$1:10 = 1\text{g}/10\text{mL} = 100 \text{ mg/mL}$$

$$0.5 \text{ mL in } 5 \text{ mL} = 10 \text{ doses}$$

$$10 \times 2.5^* \text{ mg} = 25 \text{ mg}$$

$$25\text{mg}/100\text{mg/mL} = 0.25 \text{ mL}$$

* Effective dose

Write a Prescription

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3	S. Ragweed	10	w/v	0.25	200	2.5	mg
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5	Bermuda	10,000	AU/ml				
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10	Dog AP	140	mcg/ml				
11							
12							
	Diluent						
		Total Volume		5.0			
		Injection Volume		0.5			

* Effective dose

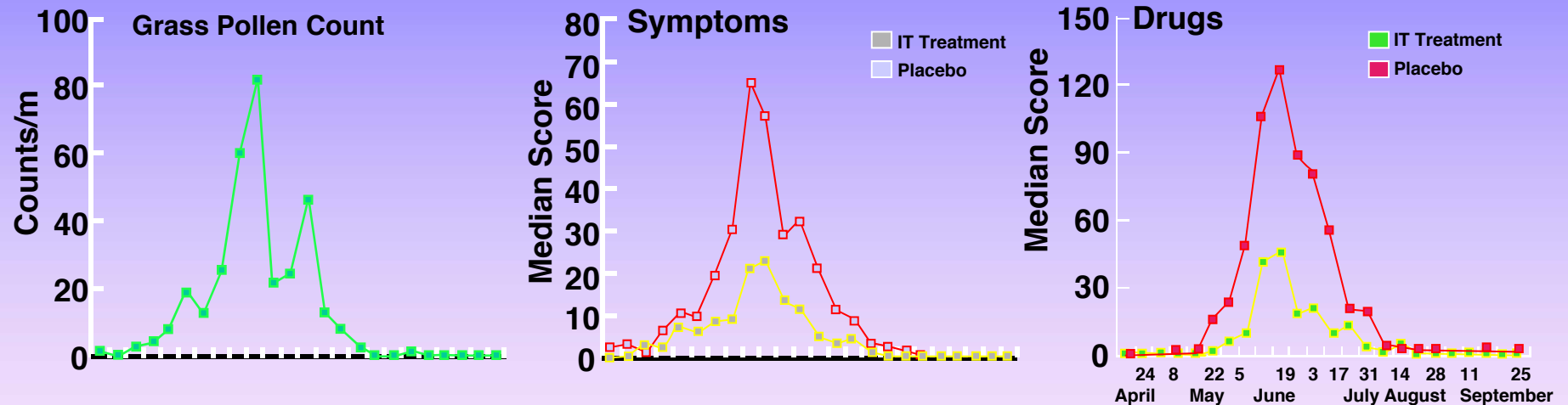
How about grass

Usefulness of Immunotherapy in Patients with Severe Summer Hay Fever Uncontrolled by Anti-allergic Drugs

Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. BMJ 1991;302:265

- 40 adults with severe grass pollen allergy uncontrolled by standard anti-allergic drugs.
- Two month immunotherapy build-up during April and May, then monthly maintenance.
- Alum adsorbed extract

Reduction in Rhinitis Symptoms and Medication Use from Immunotherapy



(Varney et al. BMJ. 1991;302:265-269.)

Efficacy and Safety of Specific Immunotherapy with SQ Allergen Extract in Treatment-resistant Seasonal allergic Rhinoconjunctivitis

- 347 adults with grass-pollen induced SAR inadequately controlled in previous year by antihistamines, topical steroids and eye drops
- Randomized to preseasonal immunotherapy with timothy grass extract high dose (20 mcg Phl p 5), low dose (2 mcg Phl p 5) or placebo

Efficacy and Safety of Specific Immunotherapy with SQ Allergen Extract in Treatment-resistant Seasonal allergic Rhinoconjunctivitis

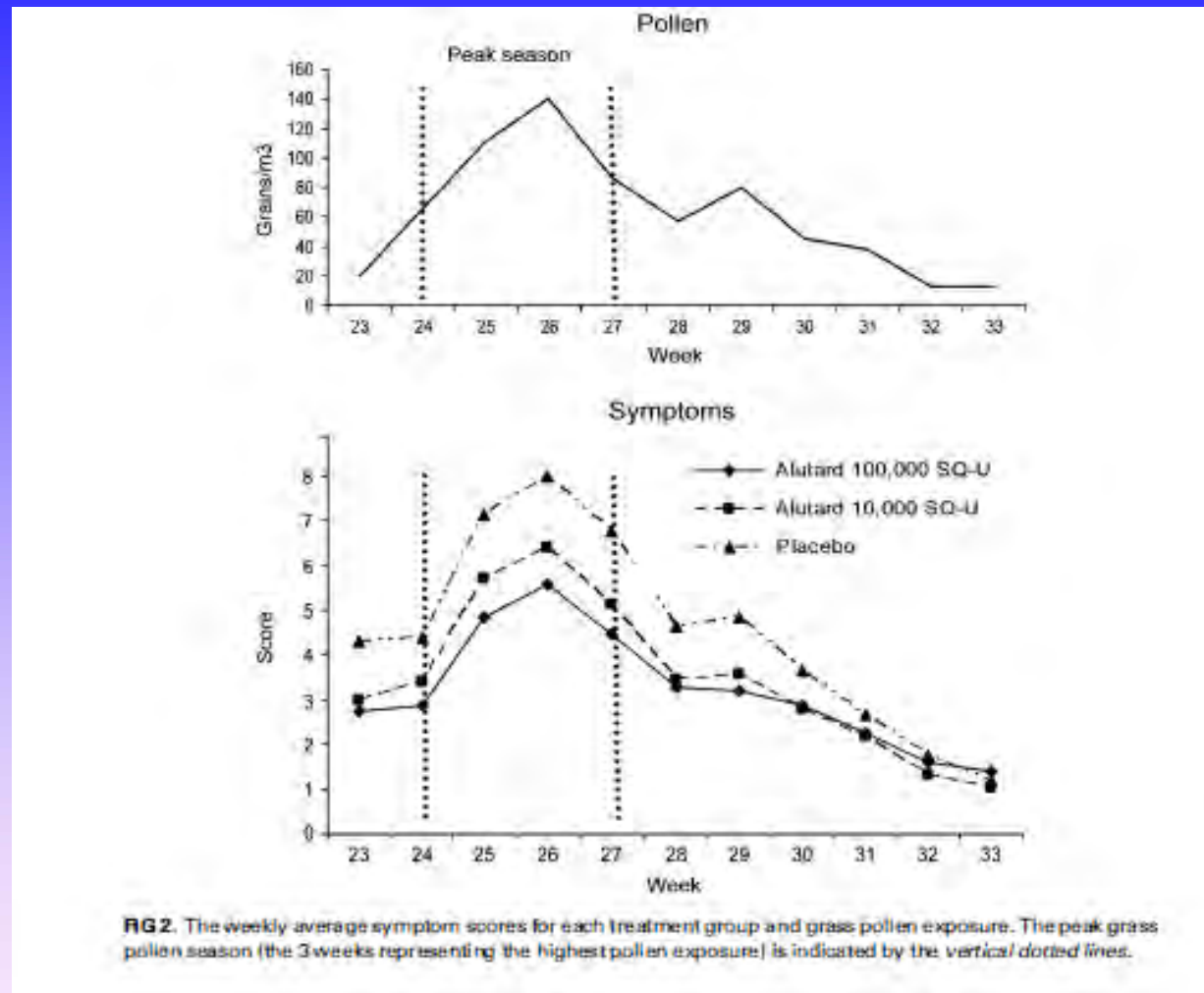
(Results compared to placebo during peak pollen period)

■

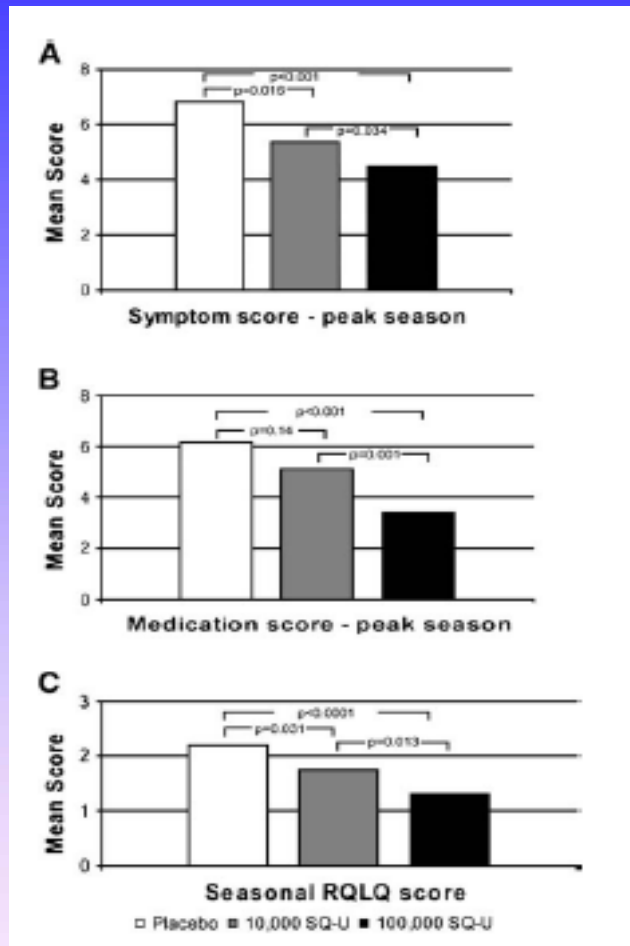
	Symptoms	Medication
High-dose timothy	- 32% (p < .0001)	- 41% (p < .0001)
Low-dose timothy	- 19% (p = .014)	- 14% (p = .16 NS)

Systemic reactions	<u>Early (urt or asthma)</u> (<u>< 1 hour</u>)	<u>late (urt, AE, or asthma)</u> (<u>1-24 hours</u>)
High-dose timothy	9 (4.4%)	39 (16%)
Low-dose timothy	0	4 (4%)
Placebo	0	2 (2%)

AJ Frew et al. J Allergy Clin Immunol 2006;117:319-25



AJ Frew et al. J Allergy Clin Immunol 2006;117:319-25



AJ Frew et al. J Allergy Clin Immunol 2006;117:319-25

A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: Clinical efficacy and side effects

Background: Seventy-four asthmatic patients allergic to house dust mite underwent double-blind, controlled study to establish the optimal maintenance dose of a standardized extract of Der p I during 24 months of IT.

Methods: 19 patients 10,000 standardized quality units (group 10, 0.7 ug Der p I), 20 patients 100,000 SQ-U (group 100, 7 ug Der p I), 16 patients 300,000 SQ-U (group 300, 21 ug Der p I), and 19 control patients (group 0) had no injections.

This study demonstrated a dose dependence of efficacy and side effects of IT in asthmatic patients. We suggest a maintenance dose of 100,000 SQ-U (7 ug Der p I) as an appropriate guideline for IT with house dust mite extract.

Haugaard et al. *J Allergy Clin Immunol.* 1993;91:709-22

Add grass to mix

Write a Prescription

- Skin test pos.

- Elm
- Maple
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- Timothy grass
- Bermuda grass
- D farinae
- B. germanica
- Alternaria
- Cat
- Dog

Vial:							
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3	S. Ragweed	10	w/v	0.25	200	2.5	mg
4	Timothy	100,000	BAU/ml	0.10	2000	1000	BAU
5	Bermuda	10,000	AU/ml				
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7	B. germanica	10	w/v				
8	Alternaria	10	w/v				
9	Cat	10,000	BAU/ml				
10	Dog AP	140	mcg/ml				
11							
12							
	Diluent						
		Total Volume					
		Injection Volume					

0.5 mL in 5 mL = 10 doses

10 x 1000 BAU* = 10,000 BAU

$\frac{10,000 \text{ BAU}}{100,000 \text{ BAU/ml}} = 0.1 \text{ mL}$

* Effective dose

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5	Bermuda	10,000	AU/ml	0.50	1000	500	AU
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		Total Volume					
		Injection Volume					

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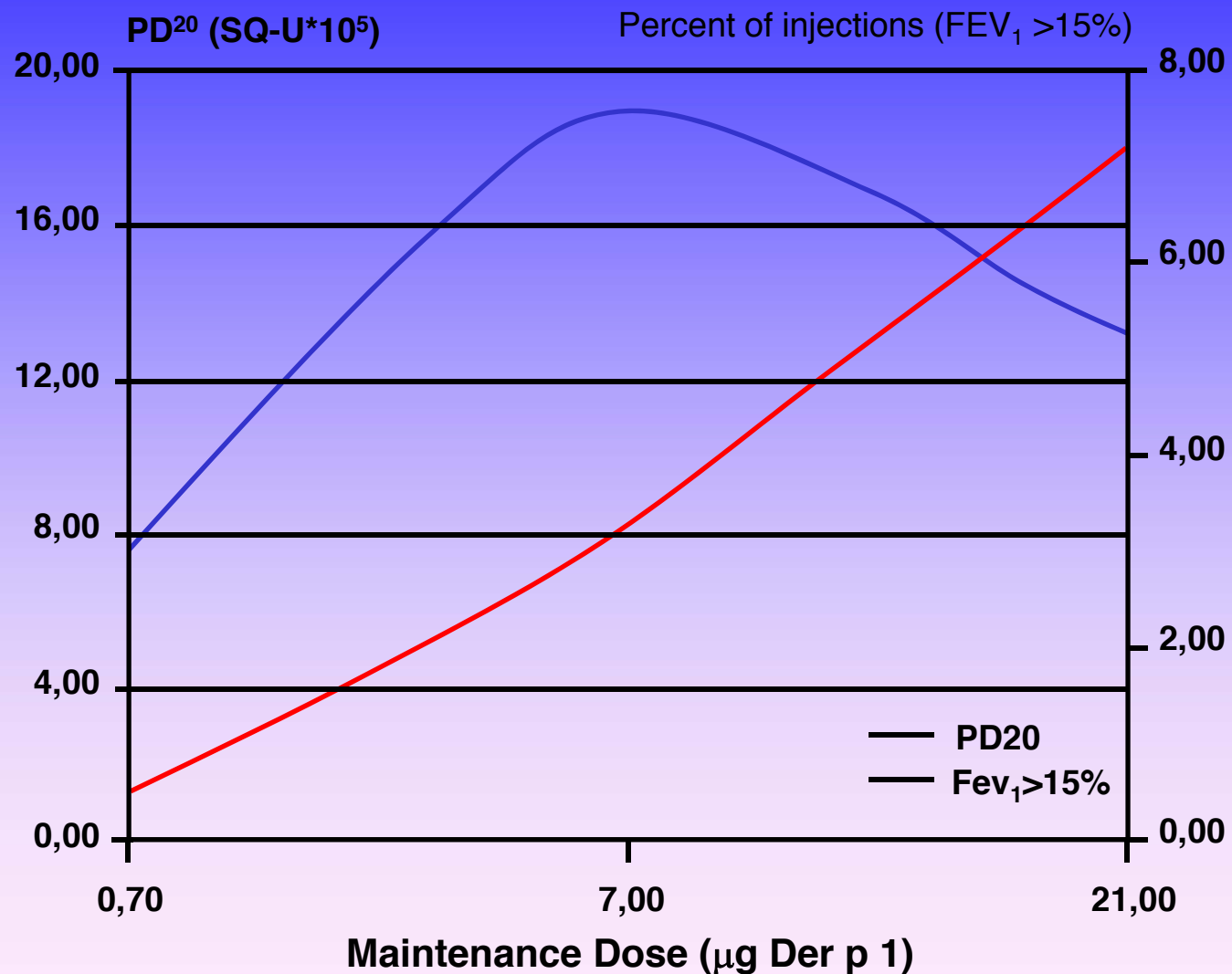
10 X 500 AU* = 5000 AU

$\frac{5000 \text{ AU}}{10,000 \text{ AU/mL}} = 0.5 \text{ mL}$

* Effective dose

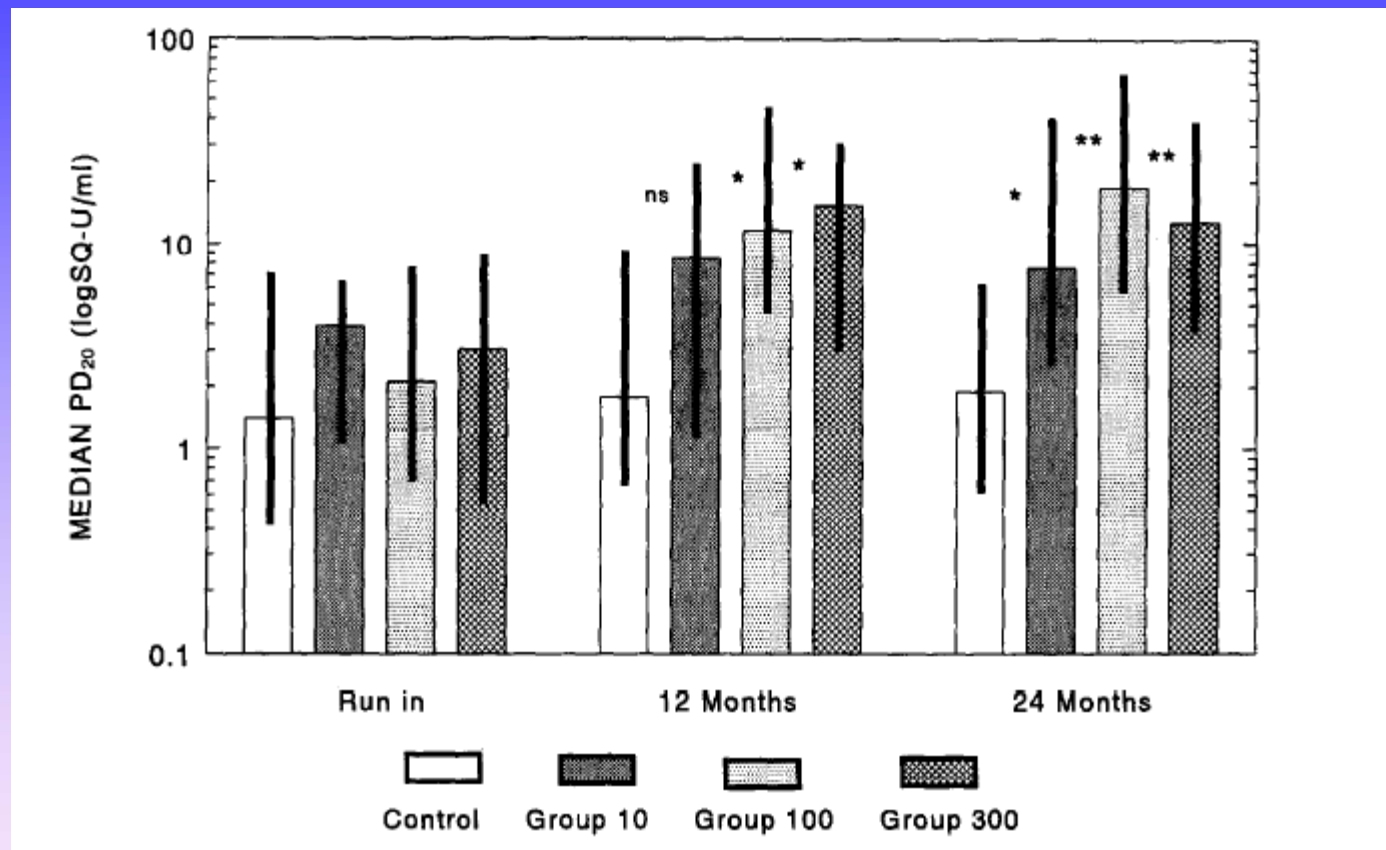
What about HDM

Dose-Response of Immunotherapy with House Dust Mites



(Haugaard et al. *J Allergy Clin Immunol.* 1993;91:709-22)

Fig 1. Changes in PD₂₀ to DP extract.



*p<0.05, **p<0.01, ***P<0.001

Haugaard et al. *J Allergy Clin Immunol.* 1993;91:709-22

Table 8: Number and distribution of injections and SR during IT

Treatment group	Total		Dose increment		Maintenance	
	No. inj	No. SRs	No. inj	No. SRs	No. inj	No. SRs
Group 10	714	4 (0.56%)	463	3 (0.65%)	251	1 (0.40%)
Group 100	754	25 (3.30%)	525	13 (2.48%)	229	12 (5.24%)
Group 300	636	45 (7.10%)	402	10 (2.49%)	234	35 (15.0%)

Haugaard et al. *J Allergy Clin Immunol.* 1993;91:709-22

A 1-Year, Placebo-Controlled, Double-Blind House-Dust-Mite Immunotherapy Study in Asthmatic Adults

OT Olsen, et al. Allergy 1997;52:853-9

- 31 house dust mite sensitive adults with asthma
- Mean age 32 years
- Maintenance dose 7 mcg Der p 1 & 10 mcg Der f 1

House Dust Mite Immunotherapy in Adults with Asthma

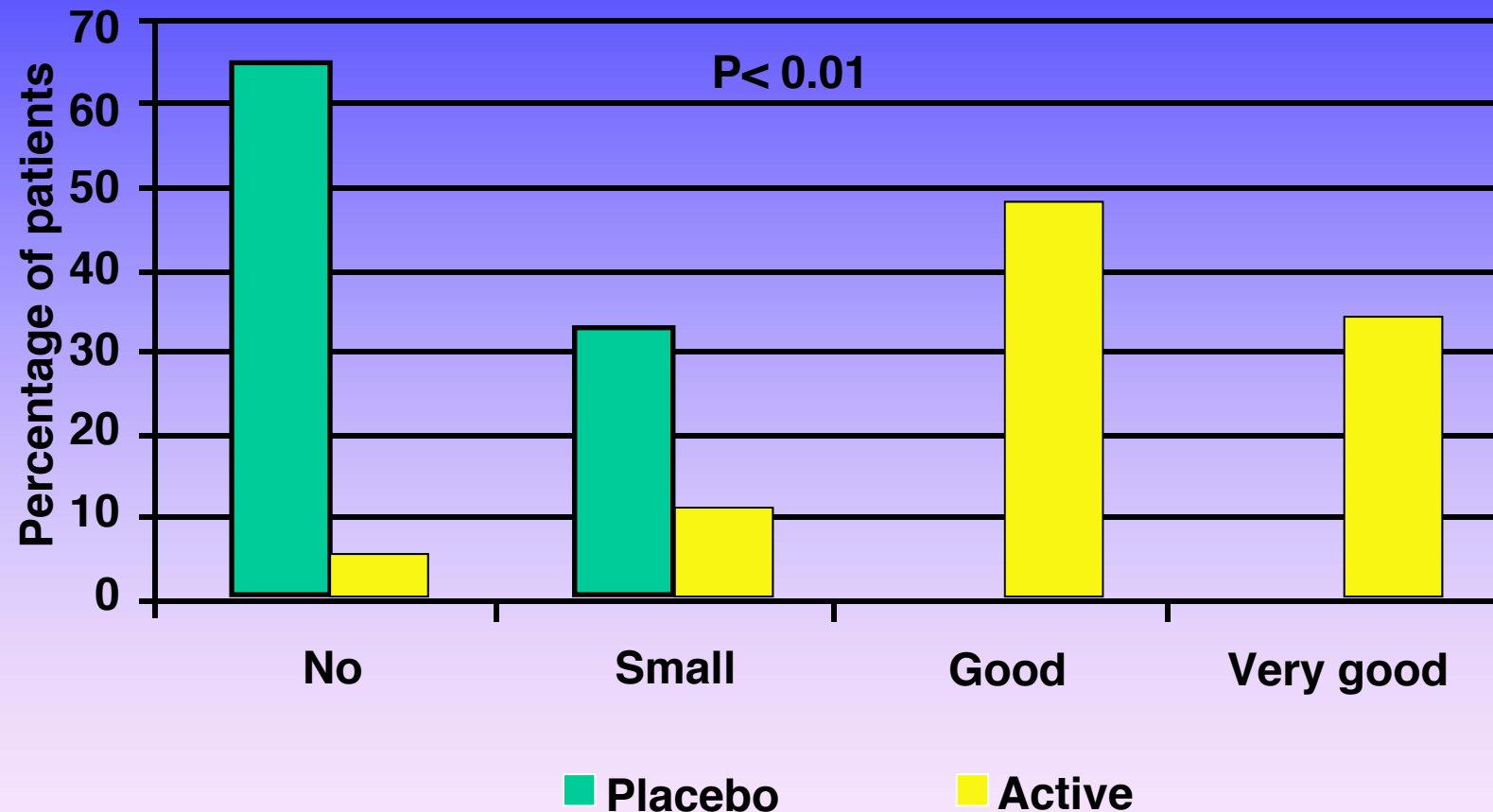
Active treatment group had significant decreases in:

- symptom scores (p<0.01)
- inhaled beta-agonists (p<0.05)
- inhaled corticosteroids (p<0.05)

increases in:

- FEV1 (p<0.01)
- FVC (p<0.02)

Patients' overall effect evaluation after treatment in Allergen-treated and placebo group.



Olsen, Allergy 1997;52:853

HDM added to IT

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6	D. farinae	10,000	AU/ml	0.50	1000	500	AU
7	B. germanica	10	w/v				
8	Alternaria	10	w/v				
9	Cat	10,000	BAU/ml				
10	Dog AP	140	mcg/ml				
11							
12							
	Diluent						
		Total Volume					
		Injection Volume					

* Effective dose

0.5 mL in 5 mL = 10 doses

10 X 500 AU* = 5000 AU

5000 AU = 0.5 mL

10,000 AU/mL

Same calculation for D. farinae

Write a Prescription

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4	Timothy	100,000	BAU/ml	0.10	2000	1000	BAU
5	Bermuda	10,000	AU/ml	0.50	1000	500	AU
6	D. farinae	10,000	AU/ml	0.50	1000	500	AU
7	B. germanica	10	w/v				
8	Alternaria	10	w/v				
9	Cat	10,000	BAU/ml				
10	Dog AP	140	mcg/ml				
11							
12							
	Diluent						
		Total Volume					
		Injection Volume					

* Effective dose

$$1:10 = 1\text{g}/10\text{mL} = 100 \text{ mg/mL}$$

$$0.5 \text{ mL in } 5 \text{ mL} = 10 \text{ doses}$$

$$10 \times 2.5^* \text{ mg} = 25 \text{ mg}$$

$$25\text{mg}/100\text{mg/mL} = 0.25 \text{ mL}$$

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12							
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How about Cat

Clinical Efficacy of Specific Immunotherapy to Cat Dander

VA Varney, et al. Clin Exp Allergy 1997;27:860-7

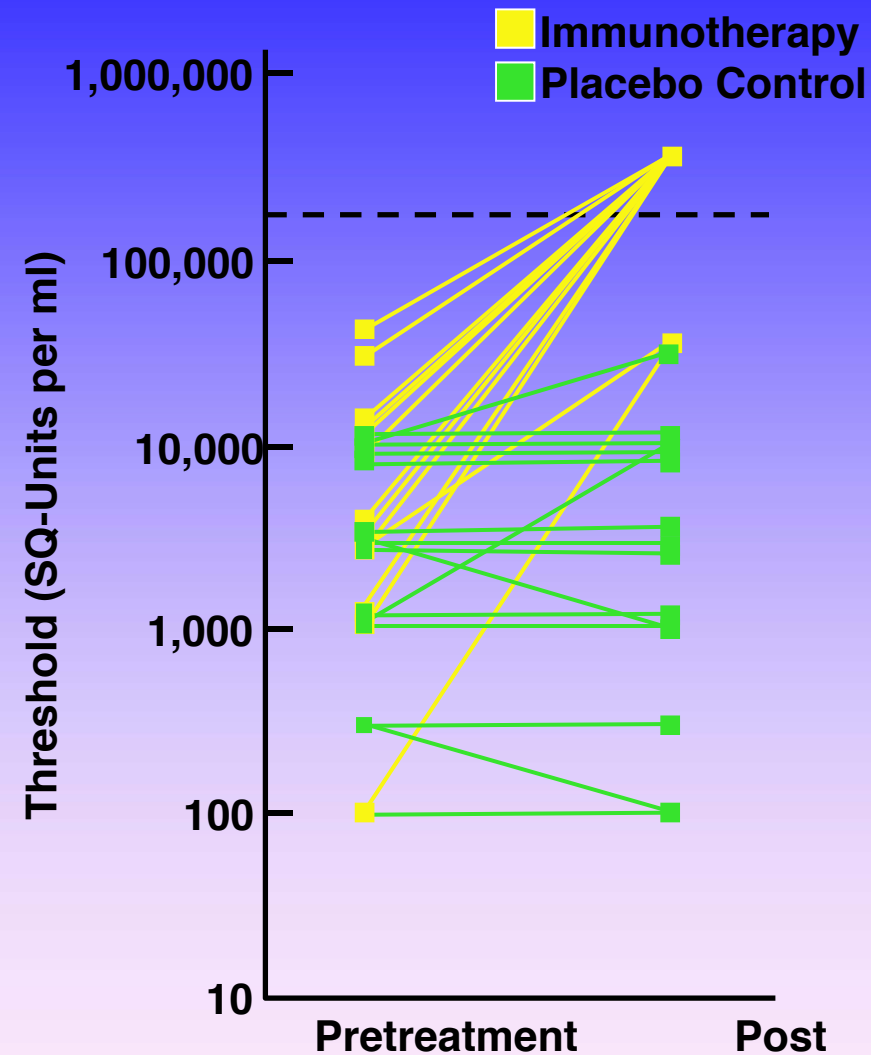
- 28 cat allergic subjects with asthma
- Treated 3 months
- Maintenance dose 15 mcg Fel d 1
- Assessed by response to house with resident cats

Immunotherapy to Cat Dander

- Active treatment group had marked reduction in sx scores following cat exposure
 - placebo 64.7 before 62.1 after
 - active 61.1 before 17.4 after ($p < 0.001$)
- Active group had reduced conjunctival and skin reactivity to cat

Varney Clin Exp Allergy 1997;27:860-7

Conjunctival Provocation Thresholds to Cat Dander Extract

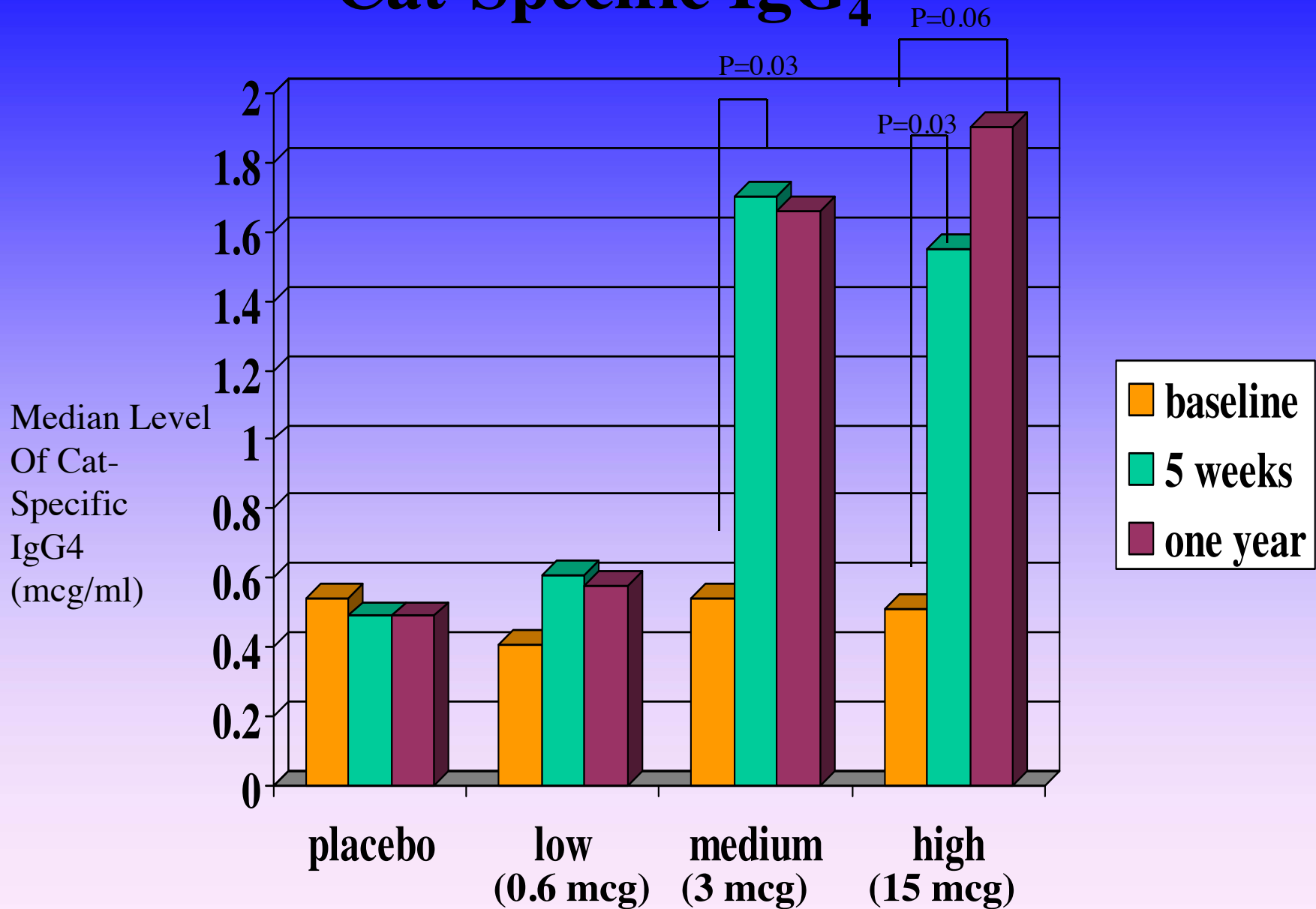


Dose Dependence and Time Course of the Immunologic Response to Administration of Standardized Cat Allergen Extract

A Nanda, et al. J.A.C.I. 2004;114:1339-44

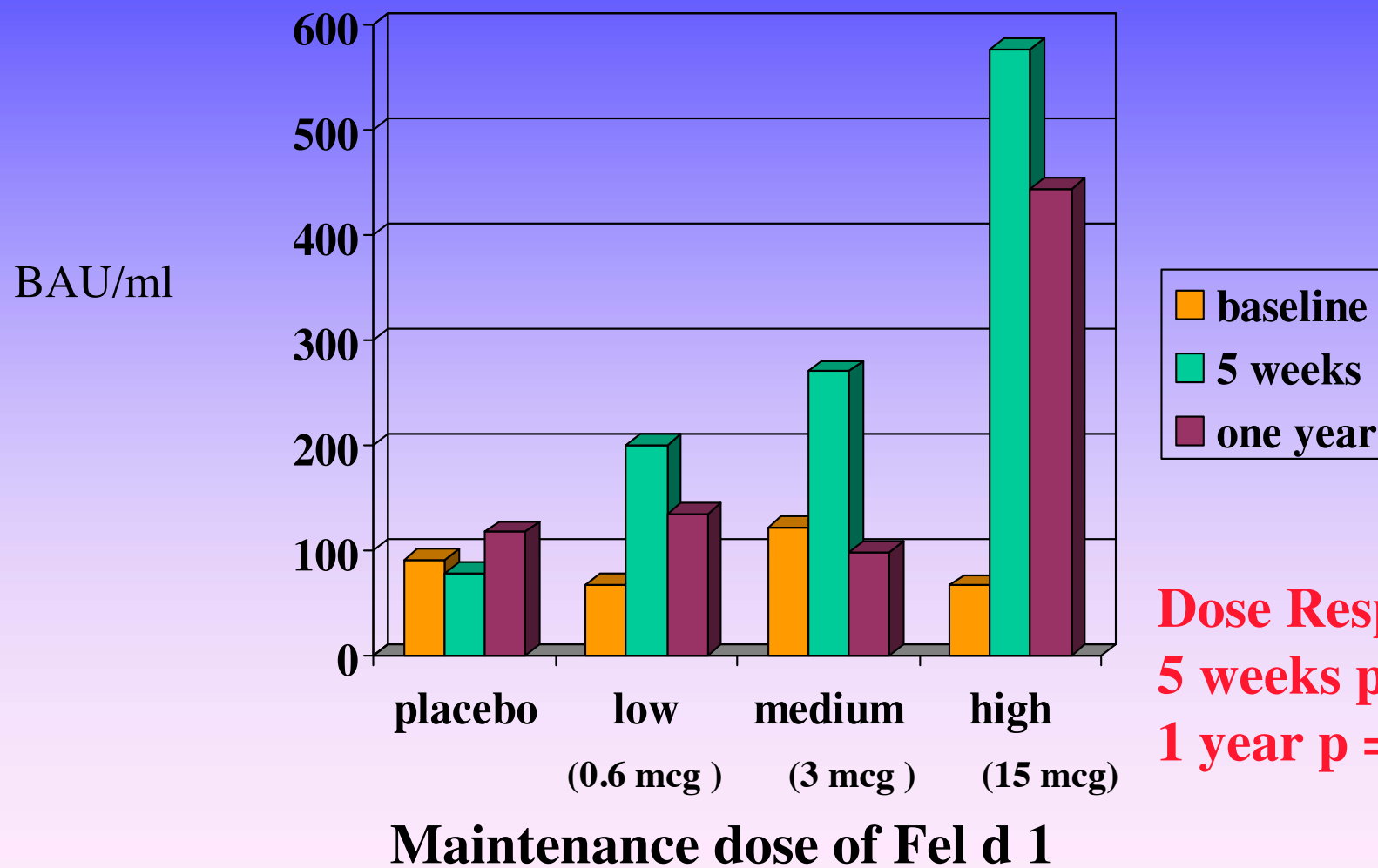
- 28 cat allergic subjects underwent cluster immunotherapy with cat dander extract achieving maintenance doses containing 0mcg, 0.6 mcg, 3.0 mcg or 15 mcg of Fel d 1 by 4 weeks.
- Immunotherapy was continued for one year.
- Immunologic assessments were performed prior to initiating immunotherapy, after the first (week 5) and one year of maintenance injections.

Cat-Specific IgG₄



Maintenance dose of Fel d 1

End Point Dose of Cat Extract of Titrated Prick Skin Tests



Conclusions

- Immunotherapy with cat dander extract containing 15 μg of Fel d 1 produces a more consistent immunologic response than one containing only 3 μg .
- The relative effectiveness of the two doses is equally manifest on first reaching maintenance at 5 weeks as after one year of maintenance injections.

Remember the importance of
effective dose

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12							
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		Total Volume					
		Injection Volume					

* Effective dose

0.5 mL in 5 mL = 10 doses
1500* BAU X 10 = 15,000 BAU

$\frac{15,000 \text{ BAU}}{10,000 \text{ BAU/mL}} = 1.5 \text{ mL}$

Probable effective dose range for allergen extracts: US units

<u>Antigen</u>	<u>Labeled potency or concentration</u>	<u>Probable effective dose range</u>
Dust mites: (D farinae and D pteronyssinus)	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed (Concentration of Amb a 1 is on the label of wt/vol extracts)	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 mg of Amb a 1 1000-4000 AU
<u>Nonstandardized extracts</u>		
dog	1:10 to 1:100 wt/vol	15 mg of Can f 1
Other extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	2.5 to 10mg Highest tolerated dose

Write a Prescription

- Skin test pos.

- Elm
- Maple
- Ragweed
- Timothy grass
- Bermuda grass
- D farinae
- B. germanica
- Alternaria
- Cat
- Dog

Vial:							
Number	Antigen	Conc of Mfr's Extract	Units	Volume added to extract	Final Concentration	Injected Dose	Units
1	Elm	10	w/v	0.25	200	2.5	mg
2	Maple	10	w/v	0.25	200	2.5	mg
3	S. Ragweed	10	w/v	0.25	200	2.5	mg
4	Timothy	100,000	BAU/ml	0.10	2000	1000	BAU
5	Bermuda	10,000	AU/ml	0.50	1000	500	AU
6	D. farinae	10,000	AU/ml	0.50	1000	500	AU
7	B. germanica	10	w/v	0.25	200	2.5	mg
8	Alternaria	10	w/v	0.25	200	2.5	mg
9	Cat	10,000	BAU/ml	1.50	3000	1500	BAU
10	Dog AP	140	mcg/ml	1.07	30	15.0	mcg
11							
12							
	Diluent						
		Total Volume					
		Injection Volume					

* Effective dose

0.5 mL in 5 mL = 10 doses

$$15 \text{ mcg}^* \times 10 = 150 \text{ mcg}$$

$$\frac{150 \text{ mcg}}{140 \text{ mcg/mL}} = 1.07 \text{ mL}$$

Major Allergen Content: U.S. Unstandardized Extracts

Extract	Conc.		Major Allergen	Content $\mu\text{g/mL}$
olive	1:10	w/v	Ole e 1	470
Birch	1:10	w/v	Bet v 1	380
Eng plant	1:10	w/v	Pla l 1	30
Brome	1:10	w/v	Group 5	215
Dog	1:10	w/v	Can f 1	5
Dog (AP)	1:100	w/v	Can f 1	140
Alternaria	1:10	w/v	Alt a 1	1 - 5
Cockroach	1:20	gly	Bla g 2	8-66*

ALK-Abello' 2004

* Jay Slater

Write a Prescription

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9	Cat	10,000	BAU/ml	1.50	3000	1500	BAU
10	Dog AP	140	mcg/ml	1.07	30	15.0	mcg
11							
12							
	Diluent			0.08			
		Total Volume		5.0			
		Injection Volume		0.5			

Final Concentrations

- Extracts dilute each other:

If X mL of an antigen is added to a vial of mixed antigens with a final volume of Y mL, then:

Final Concentration = Initial Concentration
multiplied by (X/Y)

0.5 mL of 1:10 Elm in a total of 5 mL

$$\frac{1}{10} \times \frac{0.5}{5} = \frac{1}{100}$$

Don't forget cross-reactivity

Median Dosing Recommendations by Board Certified Allergists for Immunotherapy

Allergen	Mean	25-75 %	Effective
Timothy	18.6 mcg	7.4 - 35.2 mcg	15.0 mcg
Ragweed	26.8 mcg	13.4 - 26.8 mcg	12.0 mcg
D pt	4.3 mcg	2.6 - 8.6 mcg	7.0 mcg
D far	1.0 mcg	0.6 - 2.0 mcg	10.0 mcg
Cat	1.6 mcg	1.0 - 3.0 mcg	11.0 mcg

Nelson, HS. JACI 2000;106:41

Patterns of Cross-Allergenicity Among Pollens

- There is rarely significant cross-allergenicity between families
- There is generally a degree of cross-allergenicity between tribes or genera of families
- There is generally a high degree of cross-allergenicity between species of the same genus

Cross Reactivity of Allergens

- 3 grass pollen extracts representing the cross-reacting grass pollen groups can account for essentially all of the grass allergen specificities in the United States.
 - Pooideae → meadow fescue, timothy, orchard, perennial rye, Kentucky blue, and red top grasses],
 - Chloridoideae → Bermuda grass
 - Panicoideae → Johnson grass
- Cross-reactive allergens within taxonomic groups have been identified and should serve to further consolidate allergen choices.
 - Chenopodiaceae → scales, lamb's quarter, Russian thistle, and Kochia
 - Amaranthaceae → pigweeds and Western water hemp
 - Cupressaceae → juniper, cedar, and cypress
 - Betulaceae → birch, alder, hazel
 - Fagaceae → beech and oaks
 - Oleaceae → ash, olive, and privet
 - Salicaceae → cottonwood, poplars, aspen, and willows

Significant Cross-Allergenicity Among Trees

- Birch family: birch, elder, hazelnut, hornbeam
- Olive family: European olive, ash, privet, Russian olive (botanically unrelated)
- Conifer family: cedar, cypress, juniper, arbor vitae.
- Fagaceae family: beech, oak
- Carya genus: pecan, hickory
- Populus genus: poplar, cottonwood, aspen

Use major local species for each group

Botanical Relationships Among the Grasses

- Festucoideae: Northern pasture grasses
- (timothy, orchard, June, red top, rye, etc)
- Eragrostoideae: Bermuda, grama, and several Western prairie grasses.
- Pancoideae: Bahia and Johnson grass
Use timothy +/- other NPGs (but reduce amount of each.
Use Bermuda/Bahia/Johnson if locally important

Botanical Relationships Among the Weeds

- AMBROSIA: ragweeds, cocklebur, burweed marsh elder
- ARTEMESIA: sages, wormwood, mugworts
- AMARANTHS: pigweed, western water hemp, Palmer's amaranth

Use locally important species

- CHENOPHODS: Russian thistle, kochia, lambs quarters, atriplex species
Treat both RT and Kochia if locally important

And then there is protease

Protease Content of Various Extracts

	Trypsin Equivalent
Pollens	< 1 μg
Cat & dog dander	< 1 μg
House dust mites (US)	< 5 μg
<i>Alternaria alternata</i>	29 μg
American cockroach	168 μg
<i>Aspergillus fumigatus</i>	212 μg
<i>Penicillium notatum</i>	242 μg

Robert Esch PhD, Greer Laboratories

Effect of mixing on allergen extracts.

Extract.		Alt.	Clado	PCN	CR	Mix	Mite	Overall p value
Timothy		+	-	-	+	+	-	<0.0001
Bermuda		+	-	-	-	-	-	<0.0001
Sh. ragweed		-	-	-	-	-	-	0.6371
Rus. Thistle	1st	-	-	-	+	+	-	<0.0001
	2nd	+	-	-	-	+	-	0.0065 0.0135
White oak	1st	+	-	-	-	-	-	0.0046
	2nd	-	-	-	-	+	-	0.0135
Box elder	1st	+	-	-	+	+	-	<0.0001
	2nd	-	-	-	-	-	-	0.0200
D.farinae	1st	-	-	-	-	-	-	0.0053
	2nd	-	-	-	-	-	-	0.4853
Cat	1st	-	+	-	-	-	-	0.0018
	2nd	+	-	-	-	-	-	0.0004

Alt - Alternaria, Clado = Cladosporium, PCN = Penicillium, CR = cockroach, Mix = mixture of Alt, Clado, PCN and Cr. Mite = house dust mite. 1st = first of two studies with the same Combinations, 2nd = second study

+ - p<.05 different from extract alone - p>.05 different from extract alone ND = not done

Allergenic Extract	Protease-containing Extracts			Comments
	Insects	Fungi	Mites	
Insects	Ø	⊕	⊕	Whole-body insect extracts contain very high protease levels; susceptible to endogenous proteases unless stored in 50% glycerin
Fungi	⊕	⊕	⊕	Fungal extracts do not appear to be adversely affected by proteases;
Mites	Ø	Ø	⊕	Mite allergens resistant to insect and fungal proteases if stored in ≥ 10% glycerin.
Pollens	⊗	⊗	⊕	Pollen extracts susceptible to insect and fungal proteases; compatible with mite extracts when stored in ≥ 10% glycerin.
Cat hair/epithelia	⊕	⊕	⊕	Fel d 1 in cat extract is highly resistant to fungal and insect proteases
Dog hair/epithelia	⊕	Ø	⊕	Dog allergens susceptible to most fungal extracts, but more stable when mixed with insect extracts.

Fig 1. Combinations producing low (X), moderate or risky (Ø), and favorable (+) compatibilities when allergenic extracts are mixed with protease-containing insect, fungal, and mite extracts are shown.

Esch JACI 2008;122:659-660

Allergenic Extract	Protease-containing Extracts			Comments
	Insects	Fungi	Mites	
Insects	⊗	⊕	⊕	Whole-body insect extracts contain very high protease levels; susceptible to endogenous proteases unless stored in 50% glycerin
Fungi	⊕	⊕	⊕	Fungal extracts do not appear to be adversely affected by proteases;
Mites	⊗	⊗	⊕	Mite allergens resistant to insect and fungal proteases if stored in ≥ 10% glycerin.
Pollens	⊗	⊗	⊕	Pollen extracts susceptible to insect and fungal proteases; compatible with mite extracts when stored in ≥ 10% glycerin.
Cat hair/epithelia	⊕	⊕	⊕	Fel d 1 in cat extract is highly resistant to fungal and insect proteases
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Write a Prescription

	Antigen	Conc of Mfr's Extract	Units	Volume added to extract	Final Concentration	Injected Dose	Units
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9	Cat	10,000	BAU/ml	1.50	3000	1500	BAU
10	Dog AP	140	mcg/ml	1.07	30	15.0	mcg
11							
12							
	Diluent			0.08			
	Total Volume			5.0			
	Injection Volume			0.5			

Write a Prescription: Vial #1/2

Vial:							
Number	Antigen	Conc of Mfr's Extract	Units	Volume added to extract	Final Concentration	Injected Dose	Units
1	Elm	10	w/v	0.25	200	2.5	mg
2	Maple	10	w/v	0.25	200	2.5	mg
3	S. Ragweed	10	w/v	0.25	200	2.5	mg
4	Timothy	100,000	BAU/ml	0.10	2000	1000	BAU
5	Bermuda	10,000	AU/ml	0.50	1000	500	AU
6	D. farinae	10,000	AU/ml	0.50	1000	500	AU
7	Dog AP	140	mcg/ml	1.07	30	15.0	mcg
8							
9							
10							
11							
12							
	Diluent			2.08			
		Total Volume		5.0			
		Injection Volume		0.5			

Write a Prescription: Vial #2/2

Vial:							
Number	Antigen	Conc of Mfr's Extract	Units	Volume added to extract	Final Concentration	Injected Dose	Units
1	B.germanica	10	w/v	0.25	200	2.5	mg
2	Alternaria	10	w/v	0.25	200	2.5	mg
3	Cat	10,000	BAU/ml	1.50	3000	1500	BAU
4							
5							
6							
7							
8							
9							
10							
11							
12							
	Diluent			3.0			
		Total Volume		5.0			
		Injection Volume		0.5			

Standardization

- Vials now should conform to a standardized color coding and labeling convention

Suggested nomenclature for labeling dilutions from the maintenance concentrate

<u>Dilution</u>	<u>Vol/vol</u>	<u>label No.</u>	<u>Color</u>
Maint. concentrate	1:1	1	Red
10-fold	1:10	2	Yellow
100-fold	1:100	3	Blue
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver



Preservative: 0.4% Phenol. Store at 2-8°C	Allergen Vaccine Maintenance Concentrate Expires: 06/24/01 Vial A: T,G,Rw,W 5mL Name: Joe Blow Birthdate: Oct 3, 1985 Lot: X65908-2-1	1	Allergy & Asthma Partners Kansas City, MO 64108 (816) 234-3097
Preservative: 0.4% Phenol. Store at 2-8°C	Allergen Vaccine 1:10 (v/v) Expires: 06/24/01 Vial A: T,G,Rw,W 5mL Name: Joe Blow Birthdate: Oct 3, 1985 Lot: X65908-2-1	2	Allergy & Asthma Partners Kansas City, MO 64108 (816) 234-3097
Preservative: 0.4% Phenol. Store at 2-8°C	Allergen Vaccine 1:100 (v/v) Expires: 06/24/01 Vial A: T,G,Rw,W 5mL Name: Joe Blow Birthdate: Oct 3, 1985 Lot: X65908-2-1	3	Allergy & Asthma Partners Kansas City, MO 64108 (816) 234-3097
Preservative: 0.4% Phenol. Store at 2-8°C	Allergen Vaccine 1:1000 (v/v) Expires: 06/24/01 Vial A: T,G,Rw,W 5mL Name: Joe Blow Birthdate: Oct 3, 1985 Lot: X65908-2-1	4	Allergy & Asthma Partners Kansas City, MO 64108 (816) 234-3097

Figure 2. Sample set of labels for vials containing allergen vaccine.

Expiration Dates

DILUTION	Recommended Expiration Time
Maintenance concentrate, vol/vol	6-12 Months*
1:10	6 months
1:100	6 months
1:1,000	6 weeks
1:10,000	Unknown

*The expiration date of the maintenance dose should be the expiration date of the earliest expiring constituent that is added to the mixture.

Salud

